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Patents Trademarks Designs

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International patent application PCT/EP03/09437
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14 October 2004

Our Ref:
032030WO Me/do

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Extension - 214

Responsive to the first Written Opinion drawn up by the International Preliminary Examining Authority (IPEA) dated 25 August 2004.

A new set of 11 claims is submitted, one marked-up version and one fair copy. Claims 2 and 12 have been deleted. The amended claims 1, 3, 7, 8, 10, 11 and 13 are supported by the specification. No new matter has been added.

The IPEA indicates documents relevant for the examination of the present application. Documents **D1 to D4** are listed below.

D1: WO0153312

D2: WO0112662

D3: Swall Database accession no. Q9NSS4

D4: EP-A-1188839

Item III –

The applicants amended the former claims taking into ac-

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count the objections as raised in section III by the IPEA.

Claim 2 was fused with claim 1 to reflect that said neurodegenerative disease relates to Alzheimer's disease. Thus, claim 2 was deleted.

Claim 13 was amended such as the altered staining pattern indicates a pathological state of said cell namely a pathology which relates to Alzheimer's disease.

Claims 7 and 8 were amended to clearly indicate that they are related to 'non-human' animals only.

To affirm that the methods of the instant invention as filed are related to samples which have been taken, which have been obtained from a subject the wording "obtained" was introduced into claims 1 and 13.

IPEA's additional remarks regarding **Item III** will be respond to in later stages of the national/ regional prosecution of the present application, if necessary.

Item V

Claims 10 and 11 were reworded as "Use" claims, and thus, in the light of D1, D2 and D3, subject matter of said claims is novel. Claim 12 was cancelled.
For the following reasons it is believed that claim 3 meets the criteria of novelty according to Article 33(2) PCT.

Document D1 discloses the foap-13 protein sequence among more than 1700 other protein sequences and it is not mentioned or shown, however, which are the proteins antibodies are generated, are disclosed for. Thus, a person skilled in the art will be left in the dark what are the antibodies D1 refers to.

Document D2 discloses among several other proteins the Memap-12 protein which is identical to foap-13. D2 does not refer to a specific disease, albeit D2

lists hundreds of different diseases. A person skilled in the art will not know which of the proteins disclosed will correlate with what kind of diseases listed. Quite the contrary, Table 3 of document D2 (see page 91) provides the idea that Memap-12 may be associated with cancer, inflammation/trauma and/or cell proliferation. Therefore, D2 teaches away from associating foap-13 with Alzheimer's disease. Thus, D2 does not disclose foap-13 in relation to Alzheimer's disease.

Considering the above argumentation, it is kindly requested to state novelty, inventive step and industrial applicability of the subject matter of the amended set of claims.

The Patent Attorney

(Dr. Meyers)

Enclosures: 1 set of amended claims in fair copy
1 set of amended claims in
marked-up version

AMENDED CLAIMS (marked-up version)

1. A method of diagnosing or prognosticating a neurodegenerative disease, in particular Alzheimer's disease, in a subject, or determining whether a subject is at increased risk of developing said disease, comprising:
determining a level and/or an activity of
(i) a transcription product of the foap-13 gene, and/or
(ii) a translation product of the foap-13 gene and/or
(iii) a fragment, or derivative, or variant of said transcription or translation product, in a sample obtained from said subject and comparing said level and/or said activity to a reference value representing a known disease or health status, thereby diagnosing or prognosticating said neurodegenerative disease in said subject, or determining whether said subject is at increased risk of developing said neurodegenerative disease.

~~2.The method according to claim 1 wherein said neurodegenerative disease is Alzheimer's disease.~~

~~3.~~ 2. A kit for diagnosing or prognosticating a neurodegenerative disease, in particular Alzheimer's disease, in a subject, or determining the propensity or predisposition of a subject to develop such a disease~~, said kit comprising:~~
by the steps of:
(i) detecting in a sample obtained from said subject a level, or an activity, or both said level and said activity of a transcription product and/or of a translation product of a gene coding for foap-13, and (ii) comparing said level or activity, or both said level and said activity of a transcription product and/or of a translation product of a gene coding for foap-13 to a reference value representing a known health status and/or to a reference value representing a known disease status, and said level, or activity, or both said level and said activity, of said transcription product and/or said translation product is varied compared to a reference value representing a known health status, and/or is similar or equal to a reference value representing a known disease status, said kit comprising:
a) at least one reagent which is selected from the group consisting of (i) reagents that selectively detect a transcription product of a gene coding for foap-

13 and (ii) reagents that selectively detect a translation product of a gene coding for foap-13.

~~(a)at least one reagent which is selected from the group consisting of (i) reagents that selectively detect a transcription product of the foap-13 gene and (ii) reagents that selectively detect a translation product of the foap-13 gene and~~

~~(b) an instruction for diagnosing, or prognosticating a neurodegenerative disease, in particular Alzheimer's disease, or determining the propensity or predisposition of a subject to develop such a disease by (i) detecting a level, or an activity, or both said level and said activity, of said transcription product and/or said translation product of the foap-13 gene, in a sample from said subject; and (ii) diagnosing or prognosticating a neurodegenerative disease, in particular Alzheimer's disease, or determining the propensity or predisposition of said subject to develop such a disease, wherein a varied level, or activity, or both said level and said activity, of said transcription product and/or said translation product compared to a reference value representing a known health status; or a level, or activity, or both said level and said activity, of said transcription product and/or said translation product similar or equal to a reference value representing a known disease status indicates a diagnosis or prognosis of a neurodegenerative disease, in particular Alzheimer's disease, or an increased propensity or predisposition of developing such a disease.~~

~~4.~~3. ~~-~~A modulator of an activity and/or of a level of at least one substance which is selected from the group consisting of

(i) the foap-13 gene and/or

(ii) a transcription product of the foap-13 gene and/or

(iii) a translation product of the foap-13 gene, and/or

(iv) a fragment, or derivative, or variant of (i) to (iii).

~~5.~~4. A recombinant, non-human animal comprising a non-native foap-13 gene sequence or a fragment, or a derivative, or a variant thereof, said animal being obtainable by:

(i) providing a gene targeting construct comprising said gene sequence and a selectable marker sequence, and

(ii) introducing said targeting construct into a stem cell of a non-human animal, and

(iii) introducing said non-human animal stem cell into a non-human embryo, and

(iv) transplanting said embryo into a pseudopregnant non-human animal, and

(v) allowing said embryo to develop to term, and

(vi) identifying a genetically altered non-human animal whose genome comprises a modification of said gene sequence in both alleles, and

(vii) breeding the genetically altered non-human animal of step (vi) to obtain a genetically altered non-human animal whose genome comprises a modification of said endogenous gene, wherein said disruption results in said non-human animal exhibiting a predisposition to developing symptoms of a neurodegenerative disease or related diseases or disorders.

~~6.~~5. An assay for screening for a modulator of neurodegenerative diseases, in particular Alzheimer's disease, or related diseases or disorders of one or more substances selected from the group consisting of

(i) the foap-13 gene, and/or

(ii) a transcription product of the foap-13 gene, and/or

(iii) a translation product of the foap-13 gene, and/or

(iv) a fragment, or derivative, or variant of (i) to (iii),

said method comprising:

(a) contacting a cell with a test compound;

(b) measuring the activity and/or level of one or more substances recited in (i) to (iv);

(c) measuring the activity and/or level of one or more substances recited in (i) to (iv) in a control cell not contacted with said test compound; and

comparing the levels and/or activities of the substance in the cells of step (b) and (c), wherein an alteration in the activity and/or level of substances in the contacted cells indicates that the test compound is a modulator of said diseases or disorders.

~~7.~~6. A method of screening for a modulator of neurodegenerative diseases, in particular Alzheimer's disease, or related diseases or disorders of one or more substances selected from the group consisting of

(i) the foap-13 gene, and/or

(ii) a transcription product of the foap-13 gene, and/or

(iii) a translation product of the foap-13 gene, and/or

(v) a fragment, or derivative, or variant of (i) to (iii),

said method comprising:

(a) administering a test compound to a non-human test animal which is predisposed to developing or has already developed symptoms of a neurodegenerative disease or related diseases or disorders in respect of the substances recited in (i) to (iv);

(b) measuring the activity and/or level of one or more substances recited in (i) to (iv);

(c) measuring the activity and/or level of one or more substances recited in (i) or (iv) in a matched non-human control animal which is predisposed to developing or has already developed symptoms of a neurodegenerative disease or related diseases or disorders in respect to the substances recited in (i) to (iv) and to which non-human animal no such test compound has been administered;

(d) comparing the activity and/or level of the substance in the animals of step (b) and (c), wherein an alteration in the activity and/or level of substances in the non-human test animal indicates that the test compound is a modulator of said diseases or disorders.

~~8.~~7. The method according to claim ~~7~~6 wherein said non-human test animal and/or said non-human control animal is a recombinant non-human animal which expresses foap-13, or a fragment, or a derivative, or a variant thereof, under the control of a transcriptional control element which is not the native foap-13 gene transcriptional control element.

~~9.~~8. An assay for testing a compound, preferably for screening a plurality of compounds to determine the degree of binding of said compounds to foap-13 protein, or to a fragment, or derivative, or variant thereof, said assay comprising the steps of:

(i) adding a liquid suspension of said foap-13 protein, or a fragment, or derivative, or variant thereof, to a plurality of containers;

(ii) adding a detectable, in particular a fluorescently labelled compound or a plurality of detectable, in particular fluorescently labelled compounds to be screened for said binding to said plurality of containers;

(iii) incubating said foap-13 protein, or said fragment, or derivative, or variant thereof, and said detectable, in particular fluorescently labelled compound or fluorescently labelled compounds;

(iv) measuring amounts of preferably fluorescence associated with said foap-13 protein, or with said fragment, or derivative, or variant thereof; and

(v) determining the degree of binding by one or more of said compounds to said foap-13 protein, or said fragment, or derivative, or variant thereof.

~~10.~~9. Use of a~~A~~ protein molecule, said protein molecule being a translation product of the gene coding for foap-13, SEQ ID NO. 2, or a fragment, or derivative, or variant thereof, ~~for use~~ as a diagnostic target for detecting a neurodegenerative disease, preferably Alzheimer's disease.

~~11.~~10. Use of a~~A~~ protein molecule, said protein molecule being a translation product of the gene coding for foap-13, SEQ ID NO. 2, or a fragment, or derivative, or variant thereof, ~~for use~~ as a screening target for reagents or compounds preventing, or treating, or ameliorating a neurodegenerative disease, preferably Alzheimer's disease.

~~12. An antibody specifically immunoreactive with an immunogen, wherein said immunogen is a translation product of a gene coding for foap-13, SEQ ID NO. 2, or a fragment, or derivative, or variant thereof.~~

~~13.~~11. Use of an antibody specifically immunoreactive with an immunogen, wherein said immunogen is a translation product of the gene coding for foap-13, SEQ ID NO. 2, or a fragment, or derivative, or variant thereof~~of claim 12~~, for detecting the pathological state of a cell in a sample obtained from a subject, comprising immunocytochemical staining of said cell with said antibody, wherein an altered degree of staining, or an altered staining pattern in said cell compared to a cell representing a known health status indicates a pathological state of said cell which relates to Alzheimer's disease.

AMENDED CLAIMS

1. A method of diagnosing or prognosticating a neurodegenerative disease, in particular Alzheimer's disease, in a subject, or determining whether a subject is at increased risk of developing said disease, comprising:
determining a level and/or an activity of
(i) a transcription product of the foap-13 gene, and/or
(ii) a translation product of the foap-13 gene and/or
(iii) a fragment, or derivative, or variant of said transcription or translation product, in a sample obtained from said subject and comparing said level and/or said activity to a reference value representing a known disease or health status, thereby diagnosing or prognosticating said neurodegenerative disease in said subject, or determining whether said subject is at increased risk of developing said neurodegenerative disease.

2. A kit for diagnosing or prognosticating a neurodegenerative disease, in particular Alzheimer's disease, in a subject, or determining the propensity or predisposition of a subject to develop such a diseaseby the steps of:
(i) detecting in a sample obtained from said subject a level, or an activity, or both said level and said activity of a transcription product and/or of a translation product of a gene coding for foap-13, and (ii) comparing said level or activity, or both said level and said activity of a transcription product and/or of a translation product of a gene coding for foap-13 to a reference value representing a known health status and/or to a reference value representing a known disease status, and said level, or activity, or both said level and said activity, of said transcription product and/or said translation product is varied compared to a reference value representing a known health status, and/or is similar or equal to a reference value representing a known disease status, said kit comprising:
a) at least one reagent which is selected from the group consisting of (i) reagents that selectively detect a transcription product of a gene coding for

foap-13 and (ii) reagents that selectively detect a translation product of a gene coding for foap-13.

3. A modulator of an activity and/or of a level of at least one substance which is selected from the group consisting of

(i) the foap-13 gene and/or

(ii) a transcription product of the foap-13 gene and/or

(iii) a translation product of the foap-13 gene, and/or

(iv) a fragment, or derivative, or variant of (i) to (iii).

4. A recombinant, non-human animal comprising a non-native foap-13 gene sequence or a fragment, or a derivative, or a variant thereof, said animal being obtainable by:

(i) providing a gene targeting construct comprising said gene sequence and a selectable marker sequence, and

(ii) introducing said targeting construct into a stem cell of a non-human animal, and

(iii) introducing said non-human animal stem cell into a non-human embryo, and

(iv) transplanting said embryo into a pseudopregnant non-human animal, and

(v) allowing said embryo to develop to term, and

(vi) identifying a genetically altered non-human animal whose genome comprises a modification of said gene sequence in both alleles, and

(vii) breeding the genetically altered non-human animal of step (vi) to obtain a genetically altered non-human animal whose genome comprises a modification of said endogenous gene, wherein said disruption results in said non-human animal exhibiting a predisposition to developing symptoms of a neurodegenerative disease or related diseases or disorders.

5. An assay for screening for a modulator of neurodegenerative diseases, in particular Alzheimer's disease, or related diseases or disorders of one or more substances selected from the group consisting of

(i) the foap-13 gene, and/or

(ii) a transcription product of the foap-13 gene, and/or

(iii) a translation product of the foap-13 gene, and/or

(iv) a fragment, or derivative, or variant of (i) to (iii),

said method comprising:

(a) contacting a cell with a test compound;

(b) measuring the activity and/or level of one or more substances recited in (i) to (iv);

(c) measuring the activity and/or level of one or more substances recited in (i) to (iv) in a control cell not contacted with said test compound; and

comparing the levels and/or activities of the substance in the cells of step (b) and (c), wherein an alteration in the activity and/or level of substances in the contacted cells indicates that the test compound is a modulator of said diseases or disorders.

6. A method of screening for a modulator of neurodegenerative diseases, in particular Alzheimer's disease, or related diseases or disorders of one or more substances selected from the group consisting of

(i) the foap-13 gene, and/or

(ii) a transcription product of the foap-13 gene, and/or

(iii) a translation product of the foap-13 gene, and/or

(v) a fragment, or derivative, or variant of (i) to (iii),

said method comprising:

(a) administering a test compound to a non-human test animal which is predisposed to developing or has already developed symptoms of a neurodegenerative disease or related diseases or disorders in respect of the substances recited in (i) to (iv);

(b) measuring the activity and/or level of one or more substances recited in (i) to (iv);

(c) measuring the activity and/or level of one or more substances recited in (i) or (iv) in a matched non-human control animal which is predisposed to developing or has already developed symptoms of a neurodegenerative disease or related diseases or disorders in respect to the substances recited in (i) to (iv) and to which non-human animal no such test compound has been administered;

(d) comparing the activity and/or level of the substance in the animals of step (b) and (c), wherein an alteration in the activity and/or level of substances in the non-human test animal indicates that the test compound is a modulator of said diseases or disorders.

7. The method according to claim 6 wherein said non-human test animal and/or said non-human control animal is a recombinant non-human animal which expresses foap-13, or a fragment, or a derivative, or a variant thereof, under the control of a transcriptional control element which is not the native foap-13 gene transcriptional control element.

8. An assay for testing a compound, preferably for screening a plurality of compounds to determine the degree of binding of said compounds to foap-13 protein, or to a fragment, or derivative, or variant thereof, said assay comprising the steps of:

(i) adding a liquid suspension of said foap-13 protein, or a fragment, or derivative, or variant thereof, to a plurality of containers;

(ii) adding a detectable, in particular a fluorescently labelled compound or a plurality of detectable, in particular fluorescently labelled compounds to be screened for said binding to said plurality of containers;

(iii) incubating said foap-13 protein, or said fragment, or derivative, or variant thereof, and said detectable, in particular fluorescently labelled compound or fluorescently labelled compounds;

(iv) measuring amounts of preferably fluorescence associated with said foap-13 protein, or with said fragment, or derivative, or variant thereof; and

(v) determining the degree of binding by one or more of said compounds to said foap-13 protein, or said fragment, or derivative, or variant thereof.

9. Use of a protein molecule, said protein molecule being a translation product of the gene coding for foap-13, SEQ ID NO. 2, or a fragment, or derivative, or variant thereof, as a diagnostic target for detecting a neurodegenerative disease, preferably Alzheimer's disease.

10. Use of a protein molecule, said protein molecule being a translation product of the gene coding for foap-13, SEQ ID NO. 2, or a fragment, or derivative, or variant thereof, as a screening target for reagents or compounds preventing, or treating, or ameliorating a neurodegenerative disease, preferably Alzheimer's disease.

11. Use of an antibody specifically immunoreactive with an immunogen, wherein said immunogen is a translation product of the gene coding for foap-13, SEQ ID NO. 2, or a fragment, or derivative, or variant thereof, for detecting the pathological state of a cell in a sample obtained from a subject, comprising immunocytochemical staining of said cell with said antibody, wherein an altered degree of staining, or an altered staining pattern in said cell compared to a cell representing a known health status indicates a pathological state of said cell which relates to Alzheimer's disease.